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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/349,925	07/08/99	CHANGEUX J	3495.0135-02

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EXAMINER	
KERR, J	
ART UNIT	**PAPER NUMBER**
1633	5

DATE MAILED: 09/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/349,925	Changeux et al.
Examiner	**Group Art Unit**
Janet M. Kerr	1633

☒ Responsive to communication(s) filed on *Jul 8, 1999* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *40-47* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *40-47* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Applicants' amendments, filed 7/8/99 have been entered.

Claims 1-39 have been canceled.

Claims 40-47 have been added and are being examined on the merits.

Specification

The disclosure is objected to because of the following informalities: on page 3, the reference to Changeux is incomplete, i.e., the year of publication is missing.

Appropriate correction is required.

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: TRANSGENIC MICE CONTAINING REGULATORY SEQUENCES OF THE B2-SUBUNIT OF THE NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR.

Abstract

The abstract is not entirely legible due to the quality of the copying process. It is requested that applicants submit a substitute abstract.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 40-47 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 40 is directed to a transgenic mouse comprising in its germ and somatic cells a DNA sequence comprising a specific fragment of the promoter of the β2-subunit of neuronal nicotinic acetylcholine receptor operatively linked to a nucleotide sequence encoding a heterologous polypeptide selected from a toxin, growth factor, or oncogenic, tumorigenic or immortalizing protein, which is expressed in neurons of the transgenic mouse.

Claim 41 is directed to a transgenic mouse generated by crossing a first mouse, as described in claim 40, with a second mouse, wherein the second mouse can belong to the same species as the first mouse (claim 42), the second mouse does not contain the same DNA as the first mouse (claim 43), the second mouse is a transgenic mouse that does not contain the same transgene as the first mouse (claim 44), or the second mouse contains a naturally occurring mutation not present in the first mouse (claim 45).

Claims 46 and 47 are directed to a process for producing a neuronal host cell that expresses a heterologous protein comprising transferring to the neuronal host cell a DNA sequence comprising a specific fragment of the promoter of the β2-subunit of neuronal nicotinic acetylcholine receptor operatively linked to a nucleotide sequence encoding a heterologous polypeptide (claim 46) wherein the heterologous polypeptide is selected from a toxin, growth factor, or oncogenic, tumorigenic or immortalizing protein.

The claims are not enabled as the specification fails to provide guidance and direction to the skilled artisan as to how to make and use the claimed transgenic mice. While the specification discloses transgenic mice comprising a specific promoter sequence of the β2-subunit of neuronal nicotinic acetylcholine receptor which directs expression of a heterologous nucleic acid sequence, i.e., a reporter gene, in a tissue specific manner, i.e., to certain populations of neuronal cells, and

discloses β2-subunit of neuronal nicotinic acetylcholine receptor null mice which display a particular phenotype as a function of the knock-out, the specification does not provide sufficient guidance as to which nucleotide sequences encoding the claim-designated toxins, growth factors, or oncogenic, tumorigenic, or immortalizing proteins should be used to provide transgene constructs which are stably integrated into the germ cells and somatic cells of the mouse, and which are expressed at a level such that a phenotype, which is associated with the expression of toxins, growth factors, or oncogenic, tumorigenic, or immortalizing proteins, is displayed. The specification broadly states on page 6, lines 6-10, that

"The promoter sequences are important for their ability to direct protein, polypeptide or peptide expression in certain defined cells. For example, in the transgenic mice as shown below, proteins encoding toxins or the like can be directed to neurons to mimic the degradation of those cells in disease states."

and further states on page 13, lines 18-25 that

"The regulatory elements from the nAchR β2-subunit sequences can be used to direct the neuron specific expression of a nucleotide sequence encoding a protein, polypeptide or peptide linked to them. Said protein, polypeptide or peptide can be toxins, trophic factors, neuropeptides, tumorigenic, oncogenic, or immortalizing proteins, or any other protein that can change the function of the neuron."

However, there is no disclosure in the specification as to which toxins, growth factors, or oncogenic, tumorigenic, or immortalizing proteins result in degradation of neurons, nor is there any disclosure of a correlation between a specific toxin, growth factor, or oncogenic, tumorigenic, or immortalizing protein, and a specific disease state, or a particular change of function of the neuron. In addition, with regard to expressing a toxin, there is no teaching in the specification as to the requisite level of toxin is necessary to obtain a phenotype without being lethal to the mouse.

Moreover, at the time of filing, the art of transgenics was known to be unpredictable with respect to the efficacy of incorporation of transgenes and the phenotypes expressed as a result of

the transgene incorporation. Palmiter *et al.* (Proc. Natl. Acad. Sci, USA, 1991) teach that directed expression of any gene to any specific cell type of an animal by using established transgenic methodology is theoretically possible by combining the regulatory region(s) of a gene that is expressed in a cell-specific manner with any mRNA-encoding structural gene. Palmiter *et al.* note, however, that not all gene constructs work well; the two most common problems are inappropriate expression patterns and failure to achieve adequate expression levels (see page 478, left column, first paragraph). Kappel *et al.* (Current Opinion in Biotechnology, 3:548-553, 1992) teach that while transgenes can be targeted, inherent cellular mechanisms may alter the pattern of gene expression (see, e.g., page 549, right column). In addition, Cameron (Molecular Biology, 7:253-265, 1997) teaches that

"Well-regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues....". "A feature common to many transgenic experiments is the unpredictable nature of transgene expression with different transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated...". "Such copy-number-independent, integration-site-dependent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see, e.g., page 256 under "Transgene Regulation and Expression").

In view of the lack of guidance in the specification with respect to making specific transgene constructs which encode toxins, growth factors, or oncogenic, tumorigenic, or immortalizing proteins, the lack of working examples of transgenic mice comprising the transgene constructs, and the unpredictability of producing transgenic mice which express a transgene at an appropriately level to obtain a particular phenotype, one of skill in the art would not know how to reproducibly and consistently make the transgenic mice as claimed, nor would one of skill in the art know how to use the claimed transgenic mice without knowledge of a specific phenotype.

With regard to mating transgenic mice with other mice, the specification discloses on page 8, line 24 through page 9, line 4, that

"The transgenic animals obtained with the b2-subunit gene sequence (wildtype or mutated fragments thereof) can be used to generate double transgenic animals. For this purpose the β2-subunit transgenic animal can be mated with other transgenic animals of the same species or with naturally occurring mutant animals of the same species. The resulting double transgenic animal, or cells derived from it, can be used in the same applications as the parent β2-subunit transgenic animal."

and further that

"Mutant animals are also created by mating a first transgenic animal containing the sequences described here or made available by this invention, with a second animal. The second animal can contain DNA that differs from the DNA contained in the first animal. In such a way, various lines of mutant animals can be created." (See page 9, line 26 through page 10, line 4).

However, as stated above, as there is no disclosure in the specification of any phenotype associated with the transgenic mouse, no disclosure of a phenotype associated with mice containing naturally occurring mutations, no disclosure of a phenotype associated with other transgenic mice containing a transgene which is different from the first transgenic mouse, and no disclosure of the resulting phenotypes displayed by crossing any of the aforementioned mice, one of skill in the art would not know how to use the claimed transgenic mice. Thus, for the reasons set forth above, the specification is not enabling for the claimed transgenic mice.

Claims 46 and 47 are directed to a process for producing a neuronal host cell that expresses a heterologous protein comprising transferring to the neuronal host cell a DNA sequence comprising a specific fragment of the promoter of the β2-subunit of neuronal nicotinic

acetylcholine receptor operatively linked to a nucleotide sequence encoding a heterologous polypeptide (claim 46) wherein the heterologous polypeptide is selected from a toxin, growth factor, or oncogenic, tumorigenic or immortalizing protein. As written, the claims encompass both *in vivo* and *in vitro* gene delivery. However, the specification does not disclose how to transfer the DNA sequences to neuronal host cells *in vivo*, the amount of DNA sequence to transfer such that expression of the transgene is obtained, or what the physiological effect of such transfer on the *in vivo* host cell would be. Moreover, as there are no specific examples in the specification with respect to a particular toxin, or oncogenic, tumorigenic, or immortalizing protein, one of skill in the art would not know how to use the neuronal host cells comprising the construct as there is no teaching in the specification of any particular property associated with such a transformed neuronal host cell. Given the limited guidance in the specification, the claims are non-enabling as one of skill in the art would not know how to use such a cell.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 is rendered vague and indefinite by the phrase "and wherein the neurons of the transgenic mouse express the heterologous polypeptide" because it is unclear if the phrase is referring to the transgenic mouse produced by the cross or if the phrase is referring to the first mouse which is necessarily a transgenic mouse.

Claim 43 is rendered vague and indefinite by the phrase "the DNA of the second mouse is not identical to the DNA of the first mouse" because it is unclear to which DNA applicants are referring, i.e., endogenous DNA? It is unclear if applicants intend that the second mouse is of a

different strain than the first mouse or if the second mouse is not a transgenic sibling of the first mouse.

Claim 44 is rendered vague and indefinite by the phrase "the second mouse is a transgenic mouse containing a different transgene than the first mouse" as it is unclear from the specification and the claim which transgenes are encompassed in the claim.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 40 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of copending Application No. 08/465,712. Although the conflicting claims are not identical, they are not patentably distinct from each other because the transgenic mice of copending Application No. 08/465,712 encompass the transgenic mice of the instant application. For example, the transgenic mice of copending Application No. 08/465,712 have in their germ and somatic cells a DNA sequence (SEQ ID NO: 22) comprising a promoter of the β2-subunit of neuronal nicotinic acetylcholine receptor operatively linked to a heterologous polypeptide wherein the polypeptide is expressed in neurons of the transgenic mice. In the instant application, the transgenic mice comprise the same promoter construct which is operatively linked to heterologous polypeptides wherein the heterologous polypeptides of the instant invention are toxins, or oncogenic, tumorigenic, or immortalizing proteins, and therefore,

the transgenic mice of the instant application are obvious variants of the transgenic mice claimed in copending Application No. 08/465,712.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The obviousness-type double patenting rejection is being applied even though Application No. 08/465,712 is indicated as an abandoned file due to failure to perfect the drawings, in view of the telephone interview conducted with Timothy Donaldson on 9/14/00 who indicated that applicants have submitted a petition to revive the application as the drawings had been perfected in a timely manner.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to John LeGuyader, Supervisory Primary Examiner of Art Unit 1633, at (703) 308-0447. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

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